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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,692	11/16/2000	Kuo-Fen Lee	D6233CIP	5372

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/714,692	LEE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-23 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-23 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 15 February 2008 has been entered in full. Claims 20 and 23 are amended. Claims 28-30 are added.

Please note that previously filed claims 24-27 are cancelled. In the Response of 15 February 2008, Applicant has attempted to add new claims 24-26. Thus, 37 CFR § 1.126 has been applied to renumber the claims in consecutive order. "New" claims 24-26 (filed 15 February 2008) have been renumbered as claims 28-30.

Claims 20-23 and 25-27 are under consideration in the instant application.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 20-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Villalona-Calero et al. (Ann Oncol 9: 71-77, 1998). The basis for this rejection is set forth in the Examiner's Answer of 07 November 2005 and the Office Actions of 15 November 2007, 04 March 2004, and 21 October 2003.

The claims remain rejected for reasons of record, as affirmed by the Board of Patent Appeals and Interferences in the decision dated 31 March 2006.

Applicant's arguments (15 February 2008), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

At page 3 of the Response, Applicant asserts that the phrase on page 76 recited by Villalona-Calero ("hCRF reduced water content in...brain tumor models...This effect appears [to be] a direct action on the tumor microvasculature") merely indicates that some action on the microvasculature may be affecting water content. Applicant argues that this phrase does not give any indication as to what action hCF may have on the microvasculature. Applicant indicates that this statement does not provide any indication that hCRF might affect vasculature growth. Applicant also contends that Villalona-Calero does not provide any indication to determine whether or not angiogenesis has been affected by the administration of hCRF. Applicant asserts that since the instant claims require the determination of whether angiogenesis has been inhibited, Villalona-Calero does not teach all of the claims limitations and thus does not anticipate the claims under § 102.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Villalona-Calero et al. teaches administering a corticotropin releasing factor 2 (CRFR2) agonist, specifically human corticotropin releasing factor (CRF), to individuals. Specifically, Villalona-Calero et al. teaches that human patients with primary or secondary brain tumors with evidence of edema are administered CRF intravenously, by continuous infusion (pg 72, col 1, first and second full paragraphs). Additionally, since Villalona-Calero et al. administer human CRF, a CRFR2 agonist, to the same subject population and the same tissues as recited in the claims, inhibition of angiogenesis must have been inherently occurring in the prior art of Villalona-Calero et al. (*Ex parte Novitski*, 26 USPQ2d 1389 (BPAI 1993); see also *Integra LifeSciences I Ltd. V. Merck KGaA*, (DC SCalif) 50 USPQ2d 1846)). The disclosure of Villalona-Calero et al. fully meets the terms of the claimed method because a CRFR2 agonist

(corticotropin releasing factor) inherently possesses angiogenesis-inhibiting activity. A compound and all of its properties are inseparable; they are one and the same thing and simply stating a new property of CRF does not render the claimed method of inhibiting angiogenesis of the instant application free of the art (see *In re Papesch*, CCPA 137 USPQ 43; *In re Swinehart and Sfiligoj*, 169 USPQ 226 (CCPA 1971); *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978)).

It is also noted that Villalona-Calero et al. utilize MRI scans to determine the degree of edema in patients before and after the completion of the infusion of hCRF (page 72-72 ; see also abstract). Although Villalona-Calero et al. do not specifically monitor angiogenesis with the MRI scans, it was well known at the time the invention was made that MRI scans could also be used to detect angiogenesis (Stubbs, M. Acta Oncol 38(7) : 845-853, 1999; abstract; page 846, Table 1; page 850).

The broad method steps claimed in the instant application are the same as the steps disclosed in Villalona-Calero et al. Applicant's assertion that CRFR2 agonists, such as human CRF, inhibit angiogenesis in a target tissue was already inherent in Villalona-Calero et al. If Villalona-Calero et al. would have attempted to measure the effect of human CRF on angiogenesis in brain tumor tissue, they would have uncovered it. Thus, Villalona-Calero et al. anticipate the claimed invention of the instant application. Furthermore, inherent anticipation does not require that one of ordinary skill in the art recognize an inherent feature in a prior art disclosure (*Schering Corp. v. Geneva Pharmaceuticals Inc.*, 67 USPQ2d 1664 (CAFC 2003); *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 20 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting angiogenesis in a human individual with cancer comprising administering a CRFR2 agonist to said individual, does not reasonably provide enablement for a method of inhibiting angiogenesis in a human individual with a pathophysiological condition which is not cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 28 is directed to a method of inhibiting angiogenesis in a human individual comprising administering a CRFR2 agonist, wherein said angiogenesis is inhibited in an individual having a pathophysiology condition which is not cancer. Claim 29 recites that the pathophysiological condition is a diabetic retinopathy. Claim 30 recites that the method further comprises determining whether angiogenesis has been inhibited in said individual.

The specification of the instant application teaches that angiogenesis is stimulated in CRFR2 null mutant mice because CRFR2 null mutant mice appeared to exhibit an increase in the size and number of blood vessels in various tissues" (Example 16; page 48, lines 20-21). The specification also indicated that since the CRFR2 receptor and its activity have been localized within the endothelial cell layer of blood vessels, it was hypothesized that CRFR2 may play a role in regulating angiogenesis" (page 49, lines 4). The specification discloses that

immunostaining is performed to confirm that CRFR2 null mutant mice had an increased number of blood vessels of larger size in the anterior pituitary, white adipose tissue, dorsal brain surface, large intestine, heart, small intestine, and stomach (page 50, lines 9-14; pages 53-54). The specification concludes from this experiment that "one of the roles of the CRFR2 receptor in normal mice is to mediate a CRF-induced inhibition of angiogenesis" (page 50, lines 16-18). Additionally, the specification discloses that CRFR2 appears to be involved in angiogenesis in fully developed mice rather than embryonic mice (page 51).

However, the specification does not disclose any methods or working examples to indicate that CRFR2 agonists, particularly urocortin and CRF (corticotropin releasing factor), are able to inhibit angiogenesis in any target tissue or in any individual with any pathophysiological condition other than cancer, as required by the claims. The specification only outlines a prophetic procedure for inhibition of angiogenesis in a target tissue by administration of a CRFR2 agonist (pg 8, lines 6-10; pg 25, lines 19-21; pg 26, lines 1-4). However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. There is little guidance in the specification to indicate that the administration of a CRFR2 agonist inhibits angiogenesis in individuals with any number of diverse disease states that require inhibition of angiogenesis, such diabetic retinopathy, rheumatoid arthritis, psoriasis, and endometriosis. The state of the art at the time the invention was made teaches that "differences in the expression of molecules such as CD40 and in the composition of the infiltrates between, e.g. rheumatoid arthritis lesions and solid tumors are highly suggestive of pathology-related variations in the angiogenic and inflammatory processes. Possibly, mechanisms driving the angiogenic cascade are differentially regulated depending on

the disease pathology" (Griffioen et al. Pharmacol Rev 52(2): 237-268, 2000; page 259, column 1, first full paragraph; emphasis added by the examiner). Griffioen et al. also disclose that the data obtained as of the year 2000 do not allow a definite conclusion about whether inflammation-induced angiogenesis and tumor growth-induced angiogenesis are analogous processes (page 262, column 2, first full paragraph). Griffioen et al. point out that in animal models, thrombospondin-1 inhibited tumor-induced angiogenesis but worsened the disease parameters in adjuvant-induced arthritis (page 262, column 2, first full paragraph). Griffioen et al. even state that "care should be taken in just extrapolating the knowledge on tumor angiogenesis to the situation of chronic inflammation" (page 262, column 2, first full paragraph). Relevant literature teaches that at advanced stages of diabetic retinopathy neovascularization occurs and blindness can result from abnormal fibrovascular proliferation with subsequent bleeding and retinal detachment (Simo et al. Curr Diabetes Rev2: 71-98, 2006; page 71, abstract; Figure 1). Simo et al. also discloses that diabetic retinopathy is a multifactorial and complex process in which the balance between angiogenic and antiangiogenic factors is crucial in determining the progression of the condition (Simo et al., page 71, abstract; page 88, column 1; page 83, column 2, first full paragraph).

Thus, regarding the instant application, the skilled artisan would not be able to predict that the administration of a CRFR2 agonist to an individual with cancer will have the same result (inhibition of angiogenesis) in an individual with a different condition requiring an inhibition of angiogenesis (such as diabetic retinopathy or endometriosis). The skilled artisan must resort to trial and error experimentation to determine if angiogenesis could be inhibited in an individual with a condition other than cancer. Such trial and error experimentation is considered undue.

Due to the large quantity of experimentation necessary to inhibit angiogenesis in an individual with a condition which is not cancer by administration of a CRFR2 agonist, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art (see Griffioen et al., Simo et al.), and the unpredictability of the effects of a CRFR2 agonist on angiogenesis inhibition in an individual with a condition which is not cancer, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
07 May 2008

/Bridget E Bunner/
Primary Examiner, Art Unit 1647